FORM PTO-1390 (Modified) (REV 10-95) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER: 1815

U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR): 09/937723

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/EP 00/02513	MARCH 22, 2000	MARCH 30, 1999

TITLE OF INVENTION

EQUILENINE DERIVATIVES, METHODS FOR PRODUCING THE SAME AND MEDICAMENTS CONTAINING THEM

APPLICANT(S) FOR DO/EO/US

Sigfrid SCHWARZ, Ina THIEME, Bernd UNDEUTSCH, Guenter KAUFMANN, Wolfgang ROEMER

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☐ This is an express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ☒ A copy of the International Application as filed (35 U.S.C. 371 (c) (2))
   a. ☐ is transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☒ has been transmitted by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. ☐ A copy of the International Search Report (PCT/ISA/210).
8. ☐ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371 (c)(3))
   a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ have been transmitted by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☐ have not been made and will not be made.
9. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
10. ☒ An oath or declaration of the inventor(s) (35 U.S.C. 371 (c)(4)).
11. ☐ A copy of the International Preliminary Examination Report (PCT/IPEA/409).
12. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371 (c)(5)).

Items 13 to 18 below concern document(s) or information included:

13. ☒ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
14. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
15. ☒ A **FIRST** preliminary amendment.
    A **SECOND** or **SUBSEQUENT** preliminary amendment.
16. ☐ A substitute specification.
17. ☐ A change of power of attorney and/or address letter.
18. ☒ Certificate of Mailing by Express Mail
19. ☐ Other items or information:

ET 473368018 US

410 Rec'd PCT/PTO 28 SEP 2001

U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR	INTERNATIONAL APPLICATION NO.	ATTORNEY'S DOCKET NUMBER
09/937723	PCT/EP 00/02513	1815

20. The following fees are submitted:.

BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)) :

		CALCULATIONS PTO USE ONLY
☐	Search Report has been prepared by the EPO or JPO	**$930.00**
☐	International preliminary examination fee paid to USPTO (37 CFR 1.482)	**$720.00**
☐	No international preliminary examination fee paid to USPTO (37 CFR 1.482) but international search fee paid to USPTO (37 CFR 1.445(a)(2))	**$790.00**
☒	Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2) paid to USPTO	**$1,070.00**
☐	International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(2)-(4)	**$98.00**

ENTER APPROPRIATE BASIC FEE AMOUNT =	**$1,000.00**	
Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (e)).	**$0.00**	

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total claims	9 - 20 =	0	x $18.00	**$0.00**	
Independent claims	1 - 3 =	0	x $80.00	**$0.00**	
Multiple Dependent Claims **(check if applicable)**.			☐	**$0.00**	
TOTAL OF ABOVE CALCULATIONS =				**$1,000.00**	
Reduction of 1/2 for filing by small entity, if applicable. Verified Small Entity Statement must also be filed (Note 37 CFR 1.9, 1.27, 1.28) **(check if applicable).** ☐				**$0.00**	
SUBTOTAL =				**$1,000.00**	
Processing fee of **$130.00** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (f)). +				**$0.00**	
TOTAL NATIONAL FEE =				**$1,000.00**	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31) **(check if applicable).** ☐				**$0.00**	
TOTAL FEES ENCLOSED =				**$1,000.00**	
				Amount to be: refunded	$
				charged	$

☐ A check in the amount of to cover the above fees is enclosed.

☒ Please charge my Deposit Account No. **19-4675** in the amount of **$1,000.00** to cover the above fees.
A duplicate copy of this sheet is enclosed.

☒ The Commissioner is hereby authorized to charge any fees which may be required, or credit any overpayment to Deposit Account No. **19-4675** A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

STRIKER, STRIKER & STENBY
103 EAST NECK ROAD
HUNTINGTON, NEW YORK 11743

SIGNATURE

MICHAEL J. STRIKER
NAME

27233
REGISTRATION NUMBER

SEPTEMBER 28, 2001
DATE

UNITED STATES PATENT AND TRADEMARK OFFICE

Examiner: Group: Attorney Docket # 1815

Applicant(s) : SCHWARZ, S., ET AL

Serial No. :

Filed :

For : EQUILENINE DERIVATIVES, METHODS FOR PRODUCING THE SAME AND MEDICAMENTS CONTAINING THEM

SIMULTANEOUS AMENDMENT

September 28, 2001

Honorable Commissioner of Patents and Trademarks
Washington, D.C. 20231

S I R S:

Simultaneously with filing of the above identified application please amend the same as follows:

In the Claims:

Cancel all claims without prejudice.

Substitute the claims attached hereto.

REMARKS:

This Amendment is submitted simultaneously with filing of the above identified application.

With the present Amendment applicant has amended the claims so as to eliminate their multiple dependency.

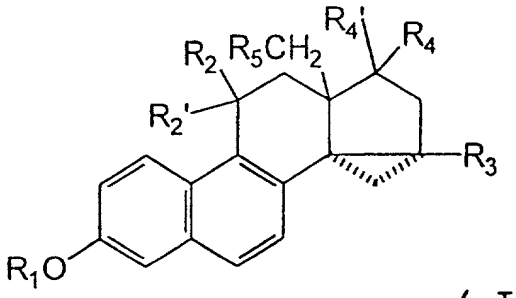
Consideration and allowance of the present application is most respectfully requested.

Respectfully submitted,

Michael J. Striker
Attorney for Applicant(s)
Reg. No. 27233

Patentansprüche

1. Equileninderivate der allgemeinen Formel I



(I) in der

R_1 ein Wasserstoffatom, eine C_1-C_5-Alkyl- oder eine C_1-C_5-Acylgruppe oder eine Benzoylgruppe bedeutet, R_2 ein Wasserstoffatom und R_2' ein Wasserstoffatom, ein Fluoratom, eine Hydroxygruppe oder eine C_1-C_5-Acyloxygruppe darstellt oder R_2 und R_2' zusammen eine Oxogruppe darstellen, R_3 ein Wasserstoffatom oder eine Methylgruppe darstellt, R_4 ein Wasserstoffatom und R_4' eine Hydroxygruppe oder eine C_1-C_{11}-Acyloxygruppe darstellt oder R_4 und R_4' zusammen eine Oxogruppe, eine Methylengruppe, eine Halogenmethylengruppe oder eine Dihalogenmethylengruppe darstellen und R_5 ein Wasserstoffatom oder eine Methylgruppe ist.

2. Equileninderivate gemäß Anspruch 1, dadurch gekennzeichnet, daß R_5 ein Wasserstoffatom ist.

3. Equileninderivate gemäß Anspruch 1, nämlich

1) 14α,15α-Methylen-estra-1,3,5(10),6,8-pentaen-3,11β,17β-triol,

2) 11β,17ß-Dihydroxy-14α,15α-methylen-estra-1,3,5(10),6,8-pentaen-3-yl-benzoat,

3) 11β,17ß-Dihydroxy-14α,15α-methylen-estra-1,3,5(10),6,8-pentaen-3-yl-propionat,

4) 3,11β-Dihydroxy-14α,15α-methylen-estra-1,3,5(10),6,8-pentaen-17ß-yl-decanoat,

5) 3,11β-Dihydroxy-14α,15α-methylen-estra-1,3,5(10),6,8-pentaen-17-on,

6) 3-Methoxy-14α,15α-methylen-estra-1,3,5(10),6,8-pentaen-11α,17ß-diyl-diacetat,

7) 15ß-Methyl-14α,15α-methylen-estra-1,3,5(10),6,8-pentaen-3,11β,17ß-triol,

8) 11β-Fluor-14α,15α-methylen-estra-1,3,5(10),6,8-pentaen-3,17ß-diol,

9) 3,17ß-Dihydroxy-14α,15α-methylen-1,3,5(10),6,8-pentaen-11-on,

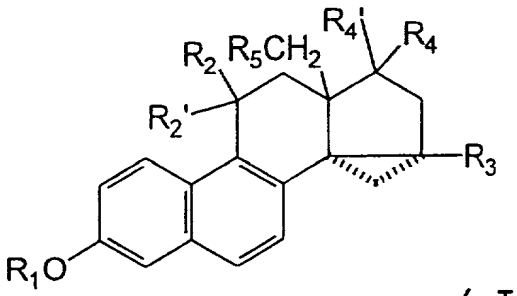
10) 3-Methoxy-14α,15α-methylen-estra-1,3,5(10),6,8-pentaen-11α,17α-diyl-diacetat,

11) 3-Methoxy-14α,15α-methylen-11-oxo-estra-1,3,5(10),6,8-pentaen-17α-yl-acetat,

12) 11β-Hydroxy-17,17-difluormethylen-14α,15α-methylen-estra-1,3,5(10),6,8-pentaen-3-yl-benzoat und

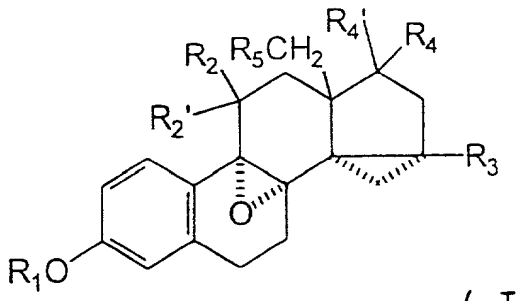
13) 14α,15α,17,17-Bis-methylen-estra-1,3,5(10),6,8-pentaen-3,11α-diol.

4. Verfahren zur Herstellung der erfindungsgemäßen Equileninderivate der allgemeinen Formel I



(I)

worin R_1, R_2, R_2', R_3, R_4, R_4' und R_5 die in Anspruch 1 gegebene Bedeutung haben, indem man eine Verbindung der allgemeinen Formel II



(II)

worin R_1, R_2, R_2', R_3, R_4, R_4' und R_5 die in Anspruch 1 gegebene Bedeutung haben, mit Diphosphortetraiodid in Gegenwart von Pyridin zur Reaktion bringt und

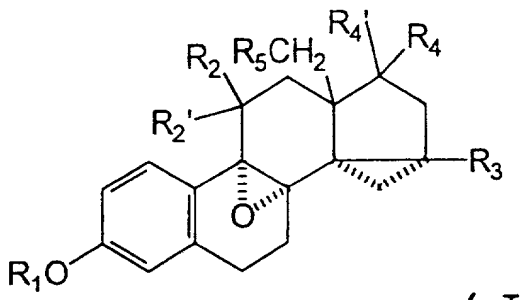
die so erhaltenen Verbindungen in an sich bekannter Weise zu den Verbindungen der allgemeinen Formel I umsetzt.

5. Pharmazeutische Zusammensetzung, die mindestens eine Verbindung der allgemeinen Formel I nach Anspruch 1, , gegebenenfalls zusammen mit pharmazeutisch verträglichen Hilfs- und Trägerstoffen enthält.

6. Verwendung der Verbindungen der allgemeinen Formel I nach Anspruch 1, zur Geroprophylaxe bei Mann und Frau.

7. Verbindungen der allgemeinen Formel I nach Anspruch 1 zur Anwendung als therapeutische Wirkstoffe.

8. Cyclopropano-Steroide der allgemeinen Formel II



(II)

worin R_1, R_2, R_2', R_3, R_4, R_4' und R_5 die in Anspruch 1 gegebene Bedeutung haben.

9. Cyclopropano-Steroide gemäß Anspruch 8, nämlich

1) 3-Methoxy-14α,15α-methylen-8α,9α-oxido-estra-1,3,5(10)-trien-17α-ol,

2) 3-Methoxy-14α,15α-methylen-8α,9α-oxido-estra-1,3,5(10)-trien-17α-yl-acetat,

3) 3-Methoxy-14α,15α-methylen-8α,9α-oxido-18a-homo-estra-1,3,5(10)-trien-17α-yl-propionat,

4) 14α,15α-Methylen-8α,9α-oxido-estra-1,3,5(10)-trien-3,17α-diyl-diacetat,

5) 3-Methoxy-15ß-methyl-14α,15α-methylen-8α,9α-oxido-estra-1,3,5(10)-trien-17ß-ol,

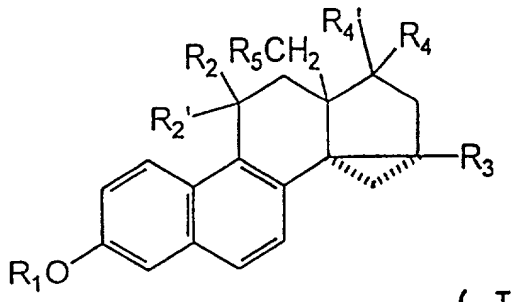
6) 11α-Hydroxy-3-methoxy-14α,15α-methylen-8α,9α-oxido-estra-1,3,5(10)-trien-17α-yl-acetat,

7) 3-Methoxy-14α,15α-methylen-8α,9α-oxido-estra-1,3,5(10)-trien-11α,17α-diyl-diacetat und

8) 3-Methoxy-11α-hydroxy-8α,9α-oxido-14α,15α-methylen-estra-1,3,5(10)-trien-17ß-yl-acetat.

PATENT CLAIMS

1. Equilenin derivatives of general formula I



(I)

wherein

R_1 denotes a hydrogen atom, a C_1-C_6-alkyl group, a C_1-C_6-acyl group or a benzoyl group,

R_2 denotes a hydrogen atom and R_2' denotes a hydrogen atom, a fluorine atom, a hydroxyl group or a C_1-C_6-acyloxy group or R_2 and R_2' together denote an oxo group,

R_3 denotes a hydrogen atom or a methyl group,

R_4 denotes a hydrogen atom and R_4' denotes a hydroxyl group or a C_1-C_{11}-acyloxy group or R_4 and R_4' together denote an oxo group, a methylene group, a halomethylene group or a dihalomethylene group and

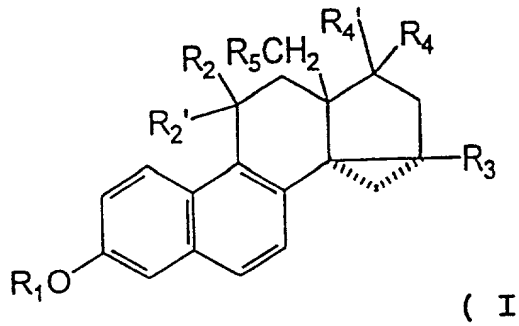
R_5 denotes a hydrogen atom or a methyl group.

2. Equilenin derivatives according to Claim 1, characterized in that R_5 is a hydrogen atom.

3. Equilenin derivatives according to Claim 1, namely

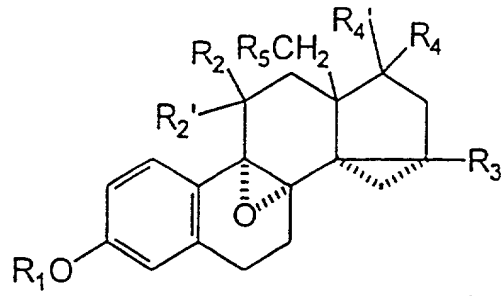
1) 14α,15α-methylenestra-1,3,5(10),6,8-pentaene-3,11β,17β-triol,
2) 11β,17β-dihydroxy-14α,15α-methylenestra-1,3,5(10),6,8-pentaen-3-yl benzoate,
3) 11β,17β-dihydroxy-14α,15α-methylenestra-1,3,5(10),6,8-pentaen-3-yl propionate,
4) 3,11β-dihydroxy-14α,15α-methylenestra-1,3,5(10),6,8-pentaen-17β-yl decanoate,
5) 3,11β-dihydroxy-14α,15α-methylenestra-1,3,5(10),6,8-pentaen-17-one,
6) 3-methoxy-14α,15α-methylenestra-1,3,5(10),6,8-pentaen-11α,17β-diyl diacetate,
7) 15β-methyl-14α,15α-methylenestra-1,3,5(10),6,8-pentaene-3,11β,17β-triol,
8) 11β-fluoro-14α,15α-methylenestra-1,3,5(10),6,8-pentaene-3,17β-diol,
9) 3,17β-dihydroxy-14α,15α-methylene-1,3,5(10),6,8-pentaen-11-one,
10) 3-methoxy-14α,15α-methylenestra-1,3,5(10),6,8-pentaen-11α,17α-diyl diacetate,
11) 3-methoxy-14α,15α-methylene-11-oxoestra-1,3,5(10),6,8-pentaen-17α-yl acetate,
12) 11β-hydroxy-17,17-difluoromethylene-14α,15α-methylenestra-1,3,5(10),6,8-pentaen-3-yl benzoate, and
13) 14α,15α-17,17-bis-methylenestra-1,3,5(10),6,8-pentaene-3,11α-diol.

4. Method for producing equilenin derivatives of the invention of general formula I



(I)

wherein R_1, R_2, R_2', R_3, R_4, R_4' and R_6 have the meaning indicated in Claim 1, by subjecting a compound of general formula II



(II)

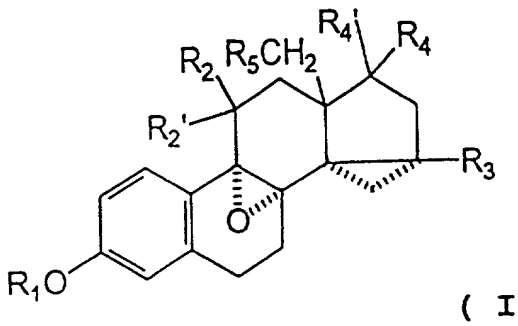
wherein R_1, R_2, R_2', R_3, R_4, R_4' and R_6 have the meaning indicated in Claim 1, to reaction with diphosphorus tetraiodide in the presence of pyridine and then converting the compound thus obtained to a compound of general formula I in a manner that in itself is known.

5. Pharmaceutical composition containing at least one compound of general formula I according to Claims 1 to 3, optionally together with pharmaceutically compatible auxiliary agents and carriers.

6. Use of the compounds of general formula I according to Claims 1 to 3 for Claim 1 geroprophylaxis in men and women.

7. Compounds of general formula I according to Claims 1 to 3 for Claim 1 use as therapeutically active substances.

8. Cyclopropano steroids of general formula II



(II)

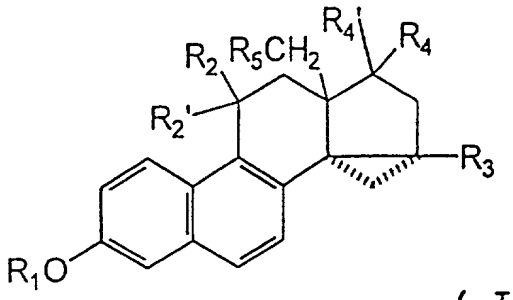
wherein R_1, R_2, R_2', R_3, R_4, R_4' and R_5 have the meaning indicated in Claim 1

9. Cyclopropano steroids according to Claim 8, namely

1) 3-methoxy-14α,15α-methylene-8α,9α-oxidoestra-1,3,5(10)-trien-17α-ol,
2) 3-methoxy-14α,15α-methylene-8α,9α-oxidoestra-1,3,5(10)-trien-17α-yl acetate,
3) 3-methoxy-14α,15α-methylene-8α,9α-oxido-18a-homoestra-1,3,5(10)-trien-17α-yl propionate,
4) 14α,15α-methylene-8α,9α-oxidoestra-1,3,5(10)-trien-3,17α-diyl diacetate,
5) 3-methoxy-15β-methyl-14α,15α-methylene-8α,9α-oxidoestra-1,3,5(10)-trien-17β-ol,
6) 11α-hydroxy-3-methoxy-14α,15α-methylene-8α,9α-oxidoestra-1,3,5(10)-trien-17α-yl acetate,
7) 3-methoxy-14α,15α-methylene-8α,9α-oxidoestra-1,3,5(10)-trien-11α,17α-diydiacetate and
8) 3-methoxy-11α-hydroxy-8α,9α-oxido-14α,15α-methylenestra-1,3,5(10)-trien-17β-yl acetate.

PATENT CLAIMS

1. Equilenin derivatives of general formula I



(I)

wherein

R_1 denotes a hydrogen atom, a C_1-C_6-alkyl group, a C_1-C_6-acyl group or a benzoyl group,

R_2 denotes a hydrogen atom and R_2' denotes a hydrogen atom, a fluorine atom, a hydroxyl group or a C_1-C_6-acyloxy group or R_2 and R_2' together denote an oxo group,

R_3 denotes a hydrogen atom or a methyl group,

R_4 denotes a hydrogen atom and R_4' denotes a hydroxyl group or a C_1-C_{11}-acyloxy group or R_4 and R_4' together denote an oxo group, a methylene group, a halomethylene group or a dihalomethylene group and

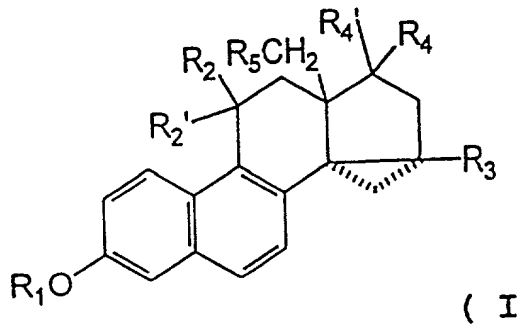
R_5 denotes a hydrogen atom or a methyl group.

2. Equilenin derivatives according to Claim 1, characterized in that R_5 is a hydrogen atom.

3. Equilenin derivatives according to Claim 1, namely

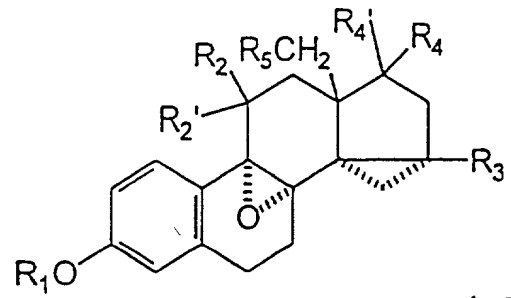
1) 14α,15α-methylenestra-1,3,5(10),6,8-pentaene-3,11β,17β-triol,
2) 11β,17β-dihydroxy-14α,15α-methylenestra-1,3,5(10),6,8-pentaen-3-yl benzoate,
3) 11β,17β-dihydroxy-14α,15α-methylenestra-1,3,5(10),6,8-pentaen-3-yl propionate,
4) 3,11β-dihydroxy-14α,15α-methylenestra-1,3,5(10),6,8-pentaen-17β-yl decanoate,
5) 3,11β-dihydroxy-14α,15α-methylenestra-1,3,5(10),6,8-pentaen-17-one,
6) 3-methoxy-14α,15α-methylenestra-1,3,5(10),6,8-pentaen-11α,17β-diyl diacetate,
7) 15β-methyl-14α,15α-methylenestra-1,3,5(10),6,8-pentaene-3,11β,17β-triol,
8) 11β-fluoro-14α,15α-methylenestra-1,3,5(10),6,8-pentaene-3,17β-diol,
9) 3,17β-dihydroxy-14α,15α-methylene-1,3,5(10),6,8-pentaen-11-one,
10) 3-methoxy-14α,15α-methylenestra-1,3,5(10),6,8-pentaen-11α,17α-diyl diacetate,
11) 3-methoxy-14α,15α-methylene-11-oxoestra-1,3,5(10),6,8-pentaen-17α-yl acetate,
12) 11β-hydroxy-17,17-difluoromethylene-14α,15α-methylenestra-1,3,5(10),6,8-pentaen-3-yl benzoate, and
13) 14α,15α-17,17-bis-methylenestra-1,3,5(10),6,8-pentaene-3,11α-diol.

4. Method for producing equilenin derivatives of the invention of general formula I



(I)

wherein R_1, R_2, R_2', R_3, R_4, R_4' and R_6 have the meaning indicated in Claim 1, by subjecting a compound of general formula II



(II)

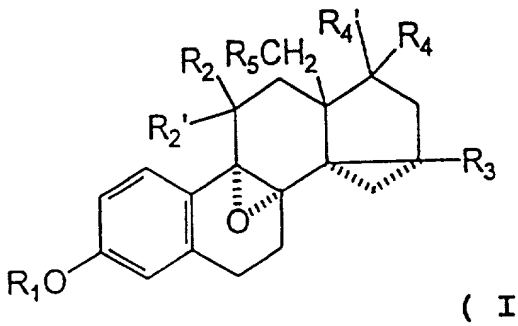
wherein R_1, R_2, R_2', R_3, R_4, R_4' and R_6 have the meaning indicated in Claim 1, to reaction with diphosphorus tetraiodide in the presence of pyridine and then converting the compound thus obtained to a compound of general formula I in a manner that in itself is known.

5. Pharmaceutical composition containing at least one compound of general formula I according to Claims 1 to 3, optionally together with pharmaceutically compatible auxiliary agents and carriers.

6. Use of the compounds of general formula I according to Claim 1 for geroprophylaxis in men and women.

7. Compounds of general formula I according to Claim 1 for use as therapeutically active substances.

8. Cyclopropano steroids of general formula II



(II)

wherein R_1, R_2, R_2', R_3, R_4, R_4' and R_5 have the meaning indicated in Claim 1

9. Cyclopropano steroids according to Claim 8, namely

1) 3-methoxy-14α,15α-methylene-8α,9α-oxidoestra-1,3,5(10)-trien-17α-ol,
2) 3-methoxy-14α,15α-methylene-8α,9α-oxidoestra-1,3,5(10)-trien-17α-yl acetate,
3) 3-methoxy-14α,15α-methylene-8α,9α-oxido-18a-homoestra-1,3,5(10)-trien-17α-yl propionate,
4) 14α,15α-methylene-8α,9α-oxidoestra-1,3,5(10)-trien-3,17α-diyl diacetate,
5) 3-methoxy-15β-methyl-14α,15α-methylene-8α,9α-oxidoestra-1,3,5(10)-trien-17β-ol,
6) 11α-hydroxy-3-methoxy-14α,15α-methylene-8α,9α-oxidoestra-1,3,5(10)-trien-17α-yl acetate,
7) 3-methoxy-14α,15α-methylene-8α,9α-oxidoestra-1,3,5(10)-trien-11α,17α-diydiacetate and
8) 3-methoxy-11α-hydroxy-8α,9α-oxido-14α,15α-methylenestra-1,3,5(10)-trien-17β-yl acetate.

Equilenin Derivatives, Methods for Producing the Same and Medicaments Containing Them

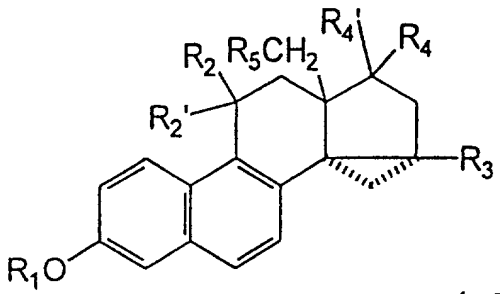
The present invention relates to novel equilenin derivatives, methods for producing the same and medicaments containing them.

Equilenin itself is an estrogenic steroid obtainable from the urine of pregnant mares.

The novel equilenin derivatives of the invention have an oxygen function on carbon atom 11 and an α-methylene bridge between carbon atoms 14 and 15. Equilenin derivatives with an oxygen function on carbon atom 11 are known. Thus, the racemic 11-oxoequilenin methyl ether was obtained by total synthesis [Tetrahedron Lett. 2763 (1967); Austr. J. Chem. 23, 547 (1970); J. Org. Chem. 39, 2193 (1974)]. A total synthetic route was also used to obtain racemic 11-oxo-3-methoxyestra-1,3,5(10),-6,8,14-hexaen-17β-ylcarboxylic acid [Tetrahedron Lett. 479 (1968)]. 14α,17α-Bridged equilenin derivatives with an 11-oxygen function were obtained by partial synthesis. The introduction of the 11-oxygen function into the molecule was achieved with Ce(IV) ammonium nitrate [Tetrahedron Lett. 35, 8599 (1994)]. Equilenin derivatives with an α- or β-methylene bridge between carbon atoms 14 and 15 have also been prepared by partial synthesis whereby the B ring was dehydrogenated with dichlorodicyanobenzoquinone (DDQ) [Tetrahedron Lett. 35, 2329 (1994)].

The object of the present invention is to provide novel equilenin derivatives and a method for producing the same.

According to the invention, this objective is reached by forming equilenin derivatives of general formula (I)



(I)

wherein

R_1 denotes a hydrogen atom, a C_1-C_6-alkyl group, a C_1-C_6-acyl group or a benzoyl group,

R_2 denotes a hydrogen atom and R_2' denotes a hydrogen atom, a fluorine atom, a hydroxyl group or a C_1-C_6-acyloxy group or R_2 and R_2' together denote an oxo group,

R_3 denotes a hydrogen atom or a methyl group,

R_4 denotes a hydrogen atom and R_4' denotes a hydroxyl group or a C_1-C_{11}-acyloxy group or R_4 and R_4' together denote an oxo group, a methylene group, a halomethylene group or a dihalomethylene group

and

R_6 denotes a hydrogen atom or a methyl group.

According to the invention, R_5 is preferably a hydrogen atom.

According to the invention, particularly preferred equilenin derivatives are, for example:

1) 14α,15α-methylenestra-1,3,5(10),6,8-pentaene-3,11β,17β-triol,
2) 11β,17β-dihydroxy-14α,15α-methylenestra-1,3,5(10),6,8-pentaen-3-yl benzoate,
3) 11β,17β-dihydroxy-14α,15α-methylenestra-1,3,5(10),6,8-pentaen-3-yl propionate,
4) 3,11β-dihydroxy-14α,15α-methylenestra-1,3,5(10),6,8-pentaen-17β-yl decanoate,
5) 3,11β-dihydroxy-14α,15α-methylenestra-1,3,5(10),6,8-pentaen-17-one,
6) 3-methoxy-14α,15α-methylenestra-1,3,5(10),6,8-pentaen-11α,17β-diyl diacetate,
7) 15β-methyl-14α,15α-methylenestra-1,3,5(10),6,8-pentaene-3,11β,17β-triol,
8) 11β-fluoro-14α,15α-methylenestra-1,3,5(10),6,8-pentaene-3,17β-diol,
9) 3,17β-dihydroxy-14α,15α-methylene-1,3,5(10),6,8-pentaen-11-one,
10) 3-methoxy-14α,15α-methylenestra-1,3,5(10),6,8-pentaen-11α,17α-diyl diacetate,
11) 3-methoxy-14α,15α-methylene-11-oxoestra-1,3,5(10),6,8-pentaen-17α-yl acetate,
12) 11β-hydroxy-17,17-difluoromethylene-14α,15α-methylenestra-1,3,5(10),6,8-pentaen-3-yl benzoate, and
13) 14α,15α-17,17-bis-methylenestra-1,3,5(10),6,8-pentaene-3,11α-diol.

For purposes of the present invention, "C_1-C_6-alkyl" means a branched or straight-chain alkyl group. Examples are the methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl or tert.butyl, n-pentyl or isopentyl groups.

For purposes of the present patent application, "C_{1-6}-acyl or C_{1-11}-acyl" means a radical of a straight-chain or branched alkanecarboxylic acid with 1 to 5 or with 1 to 11 carbon atoms, for example a radical of formic, acetic, propionic, butanoic, isobutanoic, heptanoic or undecanoic acid.

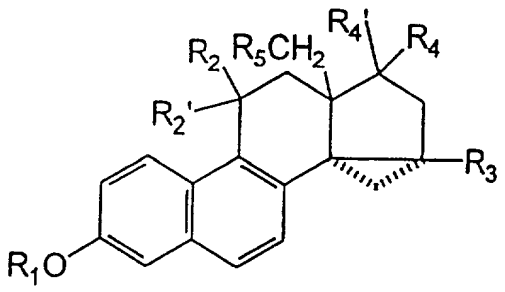
For purposes of the present invention, "halogen" means an atom of fluorine, chlorine, bromine or iodine.

The equilenin derivatives of the invention are new. Thus far, they have neither been prepared nor have their properties been described. The equilenin derivatives of the invention exhibit antioxidative activity and minor systemic hormonal action. The antioxidative activity was determined by, among other things, inhibition of iron(II)-catalyzed lipid peroxidation in synaptosomal membrane fractions of rats, by inhibition of copper(II) sulfate-induced LDL cholesterol oxidation and by inhibition of xanthine oxidase and of various other monooxygenases. The systemic estrogen action was evaluated by the Allen-Doisy test in rats. The spectrum of activity of the equilenin derivatives of the invention makes them potentially suitable for therapeutic use in all those cases in which oxygen radicals are in a causal

relationship with diseases of organs or tissues, for example in brain or spinal column injuries, states of shock, emphysema, acute respiratory distress syndrome [ARDS], ageing processes, tissue injuries after a myocardial infarction, injuries caused by intoxication or irradiation, burns and transplantation-related immune reactions, such as organ injuries in the reperfusion phase following transplantations, in spinal trauma, stroke, arteriosclerosis, ischemia, chronic-degenerative diseases of the CNS, senile dementia of the Alzheimer type (SDAT), asthma, muscular dystrophy and degenerative neurological diseases, among others, in the form of CNS intoxication or degeneration states. A preferred field of application is geroprophylaxis in women and - because the compounds of the invention exert only minor feminization action - also in men.

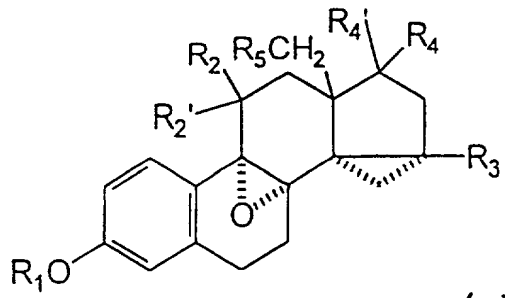
The compounds of the invention can be administered orally as well as parenterally. For oral administration, prodrugs in the form of carboxylate esters are particularly advantageous, because they provide active substance levels that remain constant for a long time.

Another object of the present invention is a method for producing the equilenin derivatives of the invention of general formula (I)



(I)

wherein R_1, R_2, R_2', R_3, R_4, R_4' and R_5 have the afore-indicated meaning, by making a compound of general formula (II)

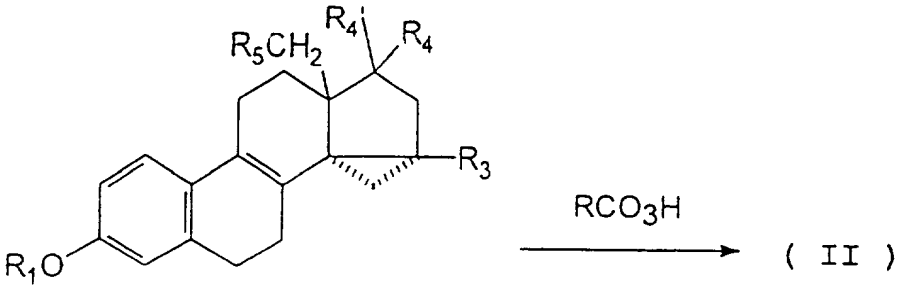


(II)

wherein R_1, R_2, R_2', R_3, R_4, R_4' and R_5 have the afore-indicated meaning, react with diphosphorus tetraiodide in the presence of pyridine, and then converting the resulting compound into a compound of general formula (I) in a manner which in itself is known.

It is known that diphosphorus tetraiodide reacts with epoxides and alcohols. Thus, epoxides can be reduced to olefins with diphosphorus tetraiodide [Synthesis 905 (1978); Nouv. J. Chem. 3, 745 (1979)]. Alcohols react with diphosphorus tetraiodide forming iodides [Tetrahedron Letters 1801 (1979); J.C.S. Chem. Commun. 229 (1983)] or with elimination to give olefins [Helv. Chim. Acta 11, 106 (1928)] or to give cumulenes [Ber. 71, 1899 (1938)]; ibid. 85, 386 (1952); ibid. 87, 598 (1954); J.C.S. Chem. Commun. 885 (1975)]. An outstanding feature of the method of the invention is that the action of diphosphorus tetraiodide on compounds of general formula (II) eliminates the 8,9-oxido group and at the same time introduces an additional double bond between carbon atoms 6 and 7. In this manner, it is possible to produce the equilenin derivatives of the invention having general formula (I) from compounds of general formula II in one step, and to avoid an additional reaction step to introduce the 6,7-double bond [Tetrahedron Letters 35, 2329 (1994)]. Another outstanding feature of the method of the invention - provided that compounds of general formula II are used wherein R_2 denotes hydrogen and R_2' stands for a hydroxyl group - is that neither elimination of the unprotected hydroxyl group to the corresponding olefin nor substitution of the hydroxyl group with iodine takes place. The course and the high selectivity of the method of the invention are surprising and could not have been predicted by someone skilled in the art.

Compounds of general formula II can be obtained from compounds of general formula III, wherein R_1 and R_3 to R_5 have the same meaning as indicated for the compounds of formula II, by treating said compounds of formula III with excess peroxycarboxylic acid

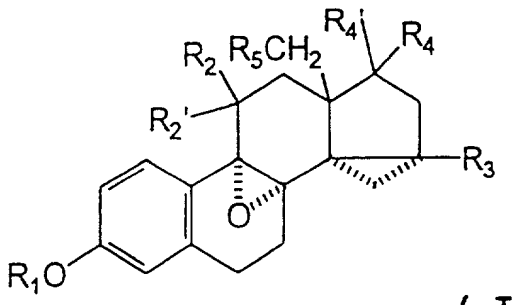


(III) (II)

Optionally, the equilenin structure of the derivatives obtained according to the invention can be further modified by methods that in themselves are known. For example, it is possible to subject compounds of general formula I, wherein R_2' denotes an α-hydroxyl group and R_2 a β-hydrogen, to oxidation with activated dimethyl sulfoxide in a known manner to form the corresponding 11-oxo compounds which can then be reduced with a complex metal hydride to form the corresponding 11β-hydroxy derivatives. Alternatively, the reaction of compounds of general formula I, wherein R_2' denotes an α-hydroxyl group and R_2 a β-hydrogen, with diethylaminosulfur trifluoride (DAST) gives compounds with an 11β-fluoro group. Compounds of general formula I, wherein R_4' denotes a C_1-C_5-alkyl group, can be converted into the free phenols with boron tribromide or diisobutylaluminum hydride in a manner which in itself is known. Compounds of general formula I, wherein R_4' denotes an α-hydroxyl group and R_4 a β-

hydrogen, can be oxidized with activated dimethyl sulfoxide in a manner which in itself is known to give the corresponding 17-oxosteroids, which upon reduction with borane or an oxazaborolidine afford 17β-hydroxy compounds.

The cyclopropano steroids of general formula II



(II)

wherein

R_1 denotes a hydrogen atom, a C_1-C_6-alkyl group, a C_1-C_6-acyl group or a benzoyl group,

R_2 denotes a hydrogen atom and R_2' a hydrogen atom, a fluorine atom, a hydroxyl group or a C_1-C_6-acyloxy group or R_2 and R_2' together denote an oxo group,

R_3 denotes a hydrogen atom or a methyl group,

R_4 denotes a hydrogen atom and R_4' denotes a hydroxyl group or a C_1-C_{11}-acyloxy group, or R_4 and R_4' together denote an oxo group, a methylene group, a halomethylene group or a dihalomethylene group and

R_5 denotes a hydrogen atom or a methyl group,

are new and have previously not been described.

Particularly preferred are, for example, the following cyclopropano steroids:

1) 3-methoxy-14α,15α-methylene-8α,9α-oxidoestra-1,3,5(10)-trien-17α-ol,
2) 3-methoxy-14α,15α-methylene-8α,9α-oxidoestra-1,3,5(10)-trien-17α-yl acetate,
3) 3-methoxy-14α,15α-methylene-8α,9α-oxido-18a-homoestra-1,3,5(10)-trien-17α-yl propionate,
4) 14α,15α-methylene-8α,9α-oxidoestra-1,3,5(10)-trien-3,17α-diyl diacetate,
5) 3-methoxy-15β-methyl-14α,15α-methylene-8α,9α-oxidoestra-1,3,5(10)-trien-17β-ol,
6) 11α-hydroxy-3-methoxy-14α,15α-methylene-8α,9α-oxidoestra-1,3,5(10)-trien-17α-yl acetate,
7) 3-methoxy-14α,15α-methylene-8α,9α-oxidoestra-1,3,5(10)-trien-11α,17α-diyl diacetate and
8) 3-methoxy-11α-hydroxy-8α,9α-oxido-14α,15α-methylenestra-1,3,5(10)-trien-17β-yl acetate.

These compounds represent novel intermediates for obtaining the equilenin derivatives of the invention and thus constitute a further object of the present invention.

The object of the present invention are also medicaments for oral, transdermal, rectal, subcutaneous, intravenous or intramuscular administration which contain a compound of general formula I as the active ingredient besides common carriers or diluents.

The medicaments of the invention are prepared in the known manner with an appropriate active substance content using common solid or liquid carriers or diluents and the commonly employed pharmaceutical auxiliary agents, depending on the route of administration desired. The preferred preparations are dosage forms suitable for oral administration. Such dosage forms are, for example, tablets, film-coated tablets, sugar-coated tablets, capsules, pills, powders, solutions, suspensions or depot forms.

Naturally, parenteral preparations such as solutions for injection are also suitable. Other suitable preparations are, for example, suppositories.

Accordingly, tablets can be obtained, for example, by mixing the active substance with known auxiliary agents, for example with an inert diluent such as dextrose, sugar, sorbitol, mannitol, polyvinylpyrrolidone, a disintegrant such as corn starch or alginic acid, a binder such as starch or gelatin, a lubricant such as magnesium stearate or talc and/or an agent for producing a depot effect, such as carboxypolymethylene, carboxymethylcellulose, cellulose acetate phthalate or polyvinyl acetate. The tablets can consist of several layers.

Coated tablets can be prepared by coating cores, prepared in the same manner as the tablets, with substances commonly used for tablet coating, for example polyvinylpyrrolidone, shellac, gum arabic, talc, titanium dioxide or sugar. The coating of the coated tablet can also consist of several layers obtained with the aid of auxiliary agents mentioned hereinabove in relation to the tablets.

Solutions or suspensions comprising the active substance of the invention can additionally contain a taste-improving agent such as saccharin, cyclamate or sugar, and also, for example, a flavoring agent such as vanillin or orange extract. They can also contain a suspension aid such as sodium carboxymethylcellulose or a preservative such as a p-hydroxybenzoate. Capsules containing an active substance can be prepared, for example, by mixing the active substance with an inert carrier, such as lactose or sorbitol, and encapsulating the mixture in gelatin capsules.

Suitable suppositories can be prepared, for example, by mixing the active substance with a carrier suitable for this purpose, for example with a neutral fat or polyethylene glycol or a derivative thereof.

A suitable dosage form is, for example, active substance-containing adhesive tape. Such systems are known.

The following examples will explain the invention.

EXAMPLE 1

11α-Hydroxy-3-methoxy-14α,15α-methylene-8α,9α-oxidoestra-1,3,5(10)-trien-17α-yl acetate from 3-methoxy-14α,15α-methylenestra-1,3,5(10),8-tetraen-17α-yl acetate

Peroxyacetic acid (32%, 5.5 mL) was added at room temperature to a solution of the tetraene steroid (3.5 g) in dichloromethane (120 mL). The reaction mixture was allowed to stand overnight at room temperature. The solution was then treated in succession with aqueous sodium thiosulfate solution (20%), saturated aqueous sodium hydrogen carbonate solution and water. The organic phase was dried over magnesium sulfate and concentrated under vacuum. The residue was subjected to flash chromatography on silica gel (eluent: cyclohexane-ethyl acetate, 3:2 v/v). Crystallization from acetone/n-hexane gave the title compound.

M.p. 159-162.5 °C. ^{1}H-NMR ($CDCl_3$/TMS[1]): 7.80 (d, J = 8.8 Hz, H-1), 6.79 (dd, J = 8.8, 2.8 Hz, H-2), 6.65 (d, J = 2.8 Hz, H-4), 4.93 (q, J = 7.9 Hz, H-11), 4.78 (d, J = 5.9 Hz, H-17), 3.80 (s, -OCH_3), 2.03 (s, -OOC-CH_3), 1.11 (dd, J = 5.4, 3.2 Hz, 14,15-CH_2-), 0.88 (s, H-18), 0.69 (ddd, J = 6.6, 5.4, 1.7 Hz, 14,15-CH_2-). MS (m/z): 354 (M^+), 336, 294, 277, 261.

EXAMPLE 2

3-Methoxy-14α,15α-methylene-8α,9α-oxidoestra-1,3,5(10)-trien-11α,17α-diyl diacetate from 11α-hydroxy-3-methoxy-14α,15α-methylene-8α,9α-oxidoestra-1,3,5(10)-trien-17α-yl acetate

Acetic anhydride (4 mL) and dimethylaminopyridine (0.04 g) were added at room temperature to a solution of the 11α-hydroxy steroid (0.4 g) in pyridine (4 mL). The mixture was stirred at room temperature for 3 hours after which it was poured into ice water. The resulting precipitate was filtered off, washed neutral with water and air-dried. Flash chromatography on silica gel (eluent: cyclohexane-ethyl acetate, 7:3 v/v) gave the title compound.

M.p. 151-154 °C. ^{1}H-NMR ($CDCl_3$/TMS): 7.80 (d, J = 8.8 Hz, H-1), 6.79 (dd, J = 8.8, 2.8 Hz, H-2), 6.65 (d, J = 2.8 Hz, H-4), 4.93 (q, J = 7.9 Hz, H-11), 4.78 (d, J = 5.9 Hz, H-17), 3.80 (s, -OCH_3), 2.03 (s, -OOC-CH_3), 1.11 (dd, J = 5.4, 3.2 Hz, 14,15-CH_2-), 0.88 (s, H-18), 0.69 (ddd, J = 6.6, 5.4, 1.7 Hz, 14,15 -CH_2-). MS (m/z): 354 (M^+) 336, 294, 277, 261.

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[1] TMS = tetramethylsilane - Translator

EXAMPLE 3

3-Methoxy-14α,15α-methylenestra-1,3,5(10),6,8-pentaen-11α,17α-diyl diacetate from
3-methoxy-14α,15α-methylene-8α,9α-oxidoestra-1,3,5(10)-trien-11α,17α-diyl diacetate

A solution consisting of the steroid diacetate (0.1 g), chloroform (2.4 mL) and pyridine (0.24 mL) was added dropwise to a stirred suspension of diphosphorus tetraiodide (0.14 g) in chloroform (2.4 mL) under argon protection. The mixture was then heated at reflux for 13 hours with agitation. Water was added, the organic phase was separated, and the aqueous phase was extracted exhaustively with chloroform. The combined organic phases were washed in succession with hydrochloric acid (1 N), water, saturated aqueous sodium hydrogen carbonate solution and saturated aqueous sodium chloride solution and then dried over magnesium sulfate and concentrated under vacuum. The residue was subjected to flash chromatography which gave the title compound.

^{1}H-NMR ($CDCl_3$/TMS): 7.66 (d, J = 8.8 Hz, H-6,7), 7.58 (d, J = 9.5 Hz, H-1), 7.17 (dd, J = 9.5, 2.8 Hz, H-2), 7.13 (d, J = 2.8 Hz, H-4), 6.85 (d, J = 8.8 Hz, H-6,7), 6.78 (q, J = 8.1 Hz, H-11), 4.98 (d, J = 6.1 Hz, H-17), 3.92 (s, -OCH_3), 2.11 (s, -OOC-CH_3), 2.09 (s, -OOC-CH_3), 1.46 (dd, J = 4.9, 3.2 Hz, 14,15-CH_2-), 0.97 (s, H-18), 0.57 (ddd, J = 8.2, 4.9, 1.7 Hz, 14,15 -CH_2-). MS (m/z): 394 (M^+), 334, 274, 259.

EXAMPLE 4

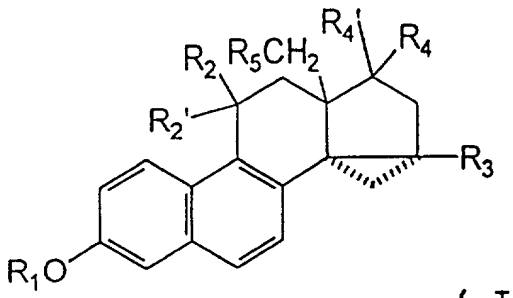
11α-Hydroxy-3-methoxy-14α,15α-methylenestra-1,3,5(10),6,8-pentaen-17α-yl acetate from
11α-hydroxy-3-methoxy-14α,15α-methylene-8α,9α-oxidoestra-1,3,5(10)-trien-17α-yl acetate

As in Example 3, the 11-hydroxy compound was treated with diphosphorus tetraiodide, which gave the title compound.

^{1}H-NMR ($CDCl_3$/TMS): 8.26 (d, J = 9.4 Hz, H-1), 7.62 (d, J = 8.3 Hz, H-6,7), 7.22 (dd, J = 9.4, 2.7 Hz, H-2), 7.12 (d, J = 2.7 Hz, H-4), 6.83 (d, J = 8.3 Hz, H-6,7), 5.68 (q, J = 7.7 Hz, H-11), 4.99 (d, J = 6.3 Hz, H-17), 3.92 (s, -OCH_3), 2.10 (s, -OOC-CH_3), 0.93 (s, H-18), 0.57 (ddd, J = 7.6, 4.8, 1.6 Hz, 14,15-CH_2-). MS (m/z): 370 (M^+), 353, 310, 292, 277, 267.

PATENT CLAIMS

1. Equilenin derivatives of general formula I



(I)

wherein

R_1 denotes a hydrogen atom, a C_1-C_5-alkyl group, a C_1-C_5-acyl group or a benzoyl group,

R_2 denotes a hydrogen atom and R_2' denotes a hydrogen atom, a fluorine atom, a hydroxyl group or a C_1-C_5-acyloxy group or R_2 and R_2' together denote an oxo group,

R_3 denotes a hydrogen atom or a methyl group,

R_4 denotes a hydrogen atom and R_4' denotes a hydroxyl group or a C_1-C_{11}-acyloxy group or R_4 and R_4' together denote an oxo group, a methylene group, a halomethylene group or a dihalomethylene group and

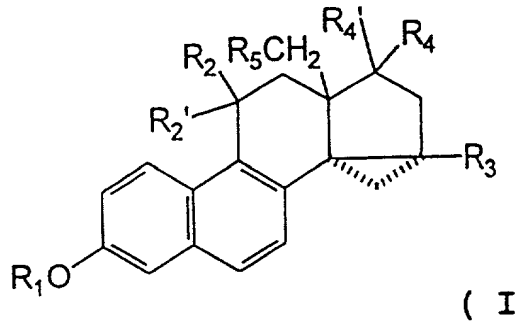
R_5 denotes a hydrogen atom or a methyl group.

2. Equilenin derivatives according to Claim 1, characterized in that R_5 is a hydrogen atom.

3. Equilenin derivatives according to Claim 1, namely

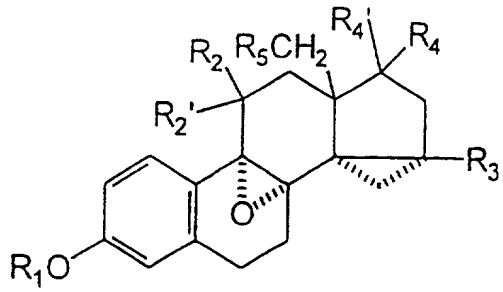
1) 14α,15α-methylenestra-1,3,5(10),6,8-pentaene-3,11β,17β-triol,
2) 11β,17β-dihydroxy-14α,15α-methylenestra-1,3,5(10),6,8-pentaen-3-yl benzoate,
3) 11β,17β-dihydroxy-14α,15α-methylenestra-1,3,5(10),6,8-pentaen-3-yl propionate,
4) 3,11β-dihydroxy-14α,15α-methylenestra-1,3,5(10),6,8-pentaen-17β-yl decanoate,
5) 3,11β-dihydroxy-14α,15α-methylenestra-1,3,5(10),6,8-pentaen-17-one,
6) 3-methoxy-14α,15α-methylenestra-1,3,5(10),6,8-pentaen-11α,17β-diyl diacetate,
7) 15β-methyl-14α,15α-methylenestra-1,3,5(10),6,8-pentaene-3,11β,17β-triol,
8) 11β-fluoro-14α,15α-methylenestra-1,3,5(10),6,8-pentaene-3,17β-diol,
9) 3,17β-dihydroxy-14α,15α-methylene-1,3,5(10),6,8-pentaen-11-one,
10) 3-methoxy-14α,15α-methylenestra-1,3,5(10),6,8-pentaen-11α,17α-diyl diacetate,
11) 3-methoxy-14α,15α-methylene-11-oxoestra-1,3,5(10),6,8-pentaen-17α-yl acetate,
12) 11β-hydroxy-17,17-difluoromethylene-14α,15α-methylenestra-1,3,5(10),6,8-pentaen-3-yl benzoate, and
13) 14α,15α-17,17-bis-methylenestra-1,3,5(10),6,8-pentaene-3,11α-diol.

4. Method for producing equilenin derivatives of the invention of general formula I



(I)

wherein R_1, R_2, R_2', R_3, R_4, R_4' and R_5 have the meaning indicated in Claim 1, by subjecting a compound of general formula II



(II)

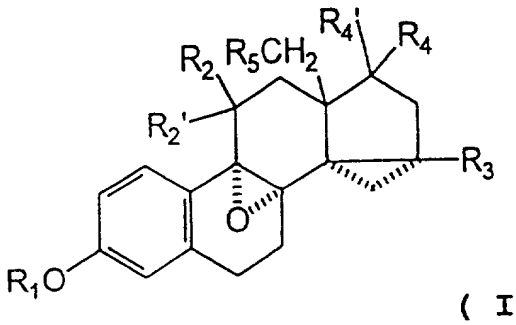
wherein R_1, R_2, R_2', R_3, R_4, R_4' and R_5 have the meaning indicated in Claim 1, to reaction with diphosphorus tetraiodide in the presence of pyridine and then converting the compound thus obtained to a compound of general formula I in a manner that in itself is known.

5. Pharmaceutical composition containing at least one compound of general formula I according to Claims 1 to 3, optionally together with pharmaceutically compatible auxiliary agents and carriers.

6. Use of the compounds of general formula I according to Claims 1 to 3 for geroprophylaxis in men and women.

7. Compounds of general formula I according to Claims 1 to 3 for use as therapeutically active substances.

8. Cyclopropano steroids of general formula II



(II)

wherein R_1, R_2, R_2', R_3, R_4, R_4' and R_5 have the meaning indicated in Claim 1

9. Cyclopropano steroids according to Claim 8, namely

1) 3-methoxy-14α,15α-methylene-8α,9α-oxidoestra-1,3,5(10)-trien-17α-ol,
2) 3-methoxy-14α,15α-methylene-8α,9α-oxidoestra-1,3,5(10)-trien-17α-yl acetate,
3) 3-methoxy-14α,15α-methylene-8α,9α-oxido-18a-homoestra-1,3,5(10)-trien-17α-yl propionate,
4) 14α,15α-methylene-8α,9α-oxidoestra-1,3,5(10)-trien-3,17α-diyl diacetate,
5) 3-methoxy-15β-methyl-14α,15α-methylene-8α,9α-oxidoestra-1,3,5(10)-trien-17β-ol,
6) 11α-hydroxy-3-methoxy-14α,15α-methylene-8α,9α-oxidoestra-1,3,5(10)-trien-17α-yl acetate,
7) 3-methoxy-14α,15α-methylene-8α,9α-oxidoestra-1,3,5(10)-trien-11α,17α-diyldiacetate and
8) 3-methoxy-11α-hydroxy-8α,9α-oxido-14α,15α-methylenestra-1,3,5(10)-trien-17β-yl acetate.

DECLARATION AND POWER OF ATTORNEY FOR NATIONAL STAGE OF PCT PATENT APPLICATION

As a below-named inventor, I hereby declare that:

Sigfrid SCHWARZ
Ina THIEME
Bernd UNDEUTSCH
Guenter KAUFMANN
Wolfgang ROEMER

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled **EQUILENIN : DERIVATIVES, METHODS FOR PRODUCING THE SAME AND MEDICAMENTS CONTAINING THEM** the specification of which was filed as PCT International Application number PCT/EP 00/02513 on March 22, 2000.

I hereby state that I believe the named inventor or inventors in this Declaration to be the original and first inventor or inventors of the subject matter which is claimed and for which a patent is sought.

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose all information which is material to the patentability of this application in accordance with Title 37, Code of Federal Regulations, Section 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, Section 119(a)-(d) or Section 365 (b) of any foreign application(s) for patent or inventor's certificate, or Section 365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate or PCT International application having a filing date before that of the application on which priority is claimed.

Prior foreign application(s):			Priority claimed:	
199 15 576.3	GERMANY	MARCH 30, 1999	X	
(Number)	(Country)	(Date filed)	Yes	No
(Number)	(Country)	(Date filed)	Yes	No

As a named inventor, I hereby appoint the following attorney to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith:

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Huntington, New York 11743
U.S.A.

I hereby declare that all statements made herein of my own knowledge are true and that all statements

made on information and belief are believed to be true; and further that these statements were made with the knowledge that wilful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such wilful false statement may jeopardize the validity of the application or any patent issued thereon.

Signature: Sigfrid Schwarz	Date: 10/14/01	Residence and Full Postal Address: Ottogerd-Muehlmannstrasse 17 D-07743 Jena Germany DEX
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Full Name of Fifth Inventor: Wolfgang ROEMER	Citizenship: GERMAN	
Signature:	Date:	Residence and Full Postal Address:
Full Name of Sixth Inventor:	Citizenship:	
Signature:	Date:	Residence and Full Postal Address:
Full Name of Seventh Inventor:	Citizenship:	

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Full Name of First or Sole Inventor: Sigfrid SCHWARZ	Citizenship: GERMAN	
Signature: Ina Thieme	Date: 10.10.2001	Residence and Full Postal Address: Siedlung 12 D-07616 Graitschen Germany DE
Full Name of Second Inventor: Ina THIEME	Citizenship: GERMAN	
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Signature:	Date: 11.10.2001	Residence and Full Postal Address: Schillbachstrasse 41 D-07743 Jena Germany DE
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Full Name of Fifth Inventor: Wolfgang ROEMER	Citizenship: GERMAN	
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Full Name of Seventh Inventor:	Citizenship:	